

REMARKS

Objection to Trademark

The Examiner has objected to a trademark in the specification as not being capitalized. The specification has been amended to capitalize the trademark and to reference it with the proper trademark symbol.

The Examiner is respectfully requested to withdraw the objection.

Objection to the Specification

The Examiner has objected to the specification for the recitation of "SEQ ID NOs4-12", and has suggested that the phrase be amended to "SEQ ID NOs:4-12" to be consistent with the remainder of the specification. The specification has been amended according to the Examiner's suggestion.

The Examiner is respectfully requested to withdraw the objection.

Rejection of Claims 6, 7 and 9 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected Claims 6, 7 and 9 under 35 U.S.C. § 112, second paragraph, contending that the phrases: "the composition is administered to the patient" in Claims 6 and 9 and "The protein or peptide is administered to a patient" in Claim 7, lack antecedent basis.

Claims 6, 7 and 9 have been amended to correct the antecedent basis. Accordingly, the Examiner is respectfully requested to withdraw the rejection of Claims 6, 7 and 9 under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 1-26 Under 35 U.S.C. § 103(a):

The Examiner has rejected Claims 1-26 under 35 U.S.C. § 103(a), contending that these claims are unpatentable over White et al. (U.S. Patent No. 5,985,261). Specifically, the Examiner contends that White et al. teach a method to treat oxidative damage in an animal by administration of a protein having a thioredoxin active site in reduced state that is effective to induce production of cellular manganese superoxide dismutase (MnSOD) that is induced by thioredoxin. The Examiner refers to the instant specification and states that this much is admitted by Applicants. The Examiner asserts that White et al. teach that the reduction of oxygen-free radicals and oxidative species would result in conditions such as lung disease, which include respiratory disease syndrome and asthma "would encompass cystic fibrosis". The Examiner further contends that White et al. teach the various doses and routes of administration presently claimed. Accordingly, the Examiner contends that the prior art teaches the use of a

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composition containing a thioredoxin active-site in reduced state effective to treat a lung disease which may include abnormal or excessive viscosity or cohesiveness of mucus or sputum because sputum is a symptom or cause of the disease including cystic fibrosis (CF). The Examiner contends that when such a symptom occurs, one of skill in the art would be motivated to use an agent taught by the art that would result in increasing liquefaction of mucus or sputum. The examiner asserts that it would have been *prima facie* obvious to treat CF and other diseases associated with abnormal or excessive viscosity or cohesiveness of mucus or sputum by increasing the liquefaction of mucus or sputum.

Applicants traverse the rejection of Claims 1-26 under 35 U.S.C. § 103 over White et al. To establish a *prima facie* case of obviousness: (1) First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) Second, there must be a reasonable expectation of success; (3) Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See also MPEP § 2143-§2143.03. An Examiner has the initial burden of establishing a *prima facie* case of obviousness before the burden shifts to the applicant to show otherwise. See, e.g., *In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). In determining obviousness, one must focus on Applicant's invention as a whole. *Symbol Technologies Inc. v. Opticon Inc.*, 19 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is:

"whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure." *In re Dow Chemical*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

Based on the required showing set forth by the Federal Circuit, Applicant contends that a *prima facie* case of obviousness has not been established in the present case.

More particularly, Applicants submit that White et al. fail to teach or suggest all the claim limitations, fail to provide the requisite motivation to arrive at the claimed invention, and fail to provide any expectation of success of making and using the claimed invention. Referring to the independent claims, Claim 1 and Claim 26 require that the composition be contacted with the mucus or sputum of the patient and that this step of contacting be sufficient to increase the liquefaction of the mucus or sputum as compared to prior to the step of contacting. White et al.

do not mention mucus or sputum at all, nor is there any connection in White et al. of thioredoxin with sputum or mucus or with any action of thioredoxin on sputum or mucus. Therefore, White et al. cannot teach or suggest that a protein or peptide having a thioredoxin active site in reduced state will have *any* effect on mucus or sputum, including that such protein or peptide could increase the liquefaction of excessively viscous or cohesive mucus or sputum. White et al. therefore do not teach or suggest that one should contact mucus or sputum with a composition comprising such protein or peptide. As set forth in the present specification, White et al. teach that thioredoxin induces MnSOD, but this is not at all related to a teaching that thioredoxin can reduce excessive viscosity or cohesiveness of mucus or sputum. The induction of MnSOD in White et al. is taught to be useful for reduce oxidative damage via the action of MnSOD. Reduction of oxidative damage is taught in White et al. to be useful in a variety of diseases and conditions, but many of the diseases and conditions described in White et al. have no association with excessively viscous or cohesive mucus or sputum (*e.g.*, ischemia reperfusion injury, rheumatoid arthritis, etc.). Accordingly, one of skill in the art cannot learn from White et al. that a protein or peptide containing a thioredoxin active site is useful for reducing excessively viscous or cohesive mucus or sputum. White et al. do not teach or suggest that one should contact the recited composition with mucus or sputum in the respiratory tract, the gastrointestinal tract or the reproductive tract of a patient. With regard to lung diseases, contrary to the Examiner's assertion, White et al. do not specifically mention cystic fibrosis as a disease to be treated, nor do "respiratory disease syndrome and asthma" encompass cystic fibrosis. Not all lung diseases are associated with excessively viscous or cohesive mucus or sputum. Moreover, even in lung diseases that are sometimes associated with excessively viscous or cohesive mucus or sputum, a patient having such disease will not always be experiencing excessively viscous or cohesive mucus or sputum. The present method is only used to contact excessively viscous or cohesive mucus or sputum in a patient. Therefore, given the disclosure of White et al., one of skill in the art would not know to select a patient that has excessively viscous or cohesive mucus or sputum, nor have any idea of when a patient that might develop excessively viscous or cohesive mucus or sputum should be treated in order to achieve the claimed result of increased liquefaction of mucus or sputum. Accordingly, White et al. do not teach the limitations of Claim 1 or Claim 26.

Moreover, there is absolutely no motivation in White et al. to use a protein or peptide comprising a thioredoxin active site in reduced state to increase the liquefaction of excessively viscous or cohesive mucus or sputum. "In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the

reference before him to make the proposed substitution, combination, or other modification.” *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). As discussed above, there is simply no teaching or suggestion in White et al. of any connection between thioredoxin and mucus or sputum, and so the reference teachings are completely insufficient to motivate one to attempt to use thioredoxin to increase liquefaction of mucus or sputum. One would not be motivated from White et al. to select this particular patient nor to treat such a patient by contacting the mucus or sputum with the recited composition until the recited effect is achieved. Moreover, the listing of diseases in White et al. in which oxidative damage may be reduced would not motivate one of normal skill in the art to attempt to use the recited composition in diseases characterized by excessive mucous, since diseases listed in White et al. are either not exclusively or primarily characterized by excessively viscous or cohesive mucus or sputum, or are not at all so characterized.

With respect to an expectation of success, Applicants submit that one of skill in the art cannot have any expectation of success from White et al. at increasing the liquefaction of excessively viscous mucus or sputum using a protein or peptide having a thioredoxin active site in reduced state, because there is no teaching whatsoever in White et al. that such protein or peptide could have such an effect. One cannot have an expectation of success at achieving a result if one does not understand that such result is possible. Nor can one expect to be able to select the recited patient (*i.e.*, a patient having excessively viscous or cohesive mucus or sputum) or choose to administer the composition in the recited manner (*i.e.*, contacting the excessively viscous or cohesive mucus or sputum) if one does not know that the composition can be used for the claimed purpose (*i.e.*, increasing liquefaction of the mucus or sputum).

Accordingly, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to Claims 1-15 and 26.

With regard to Claim 16, there is no teaching in White et al. of a composition that comprises (a) a protein or peptide containing a thioredoxin active-site in reduced state and (b) at least one additional agent for *treatment of excessively viscous or cohesive mucus or sputum*. The Examiner has not pointed to any such teaching in White et al., nor has the Examiner explained how one of skill in the art would be motivated to provide such an agent, since White et al. does not even mention mucus or sputum, let alone teach or suggest that a protein or peptide containing a thioredoxin active site in reduced state could be effective to liquefy excessively viscous or cohesive mucus or sputum. Furthermore, the Examiner has not explained how one of skill in the art would expect success at increasing liquefaction of excessively viscous or cohesive mucus or sputum, when White et al. clearly has no appreciation that thioredoxin or a related protein or

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peptide could have any such effect on mucus or sputum. One of skill in the art would have absolutely no basis to provide the composition as recited in Claims 16-25 in view of White et al.

Accordingly, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to Claims 16-25.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-26 under 35 U.S.C. § 103(a).

Applicants have attempted to respond to all of the issues raised by the Examiner in the March 13 Office Action and submit that the claims are in a condition for allowance. Any questions or concerns regarding Applicants' position should be directed to the below-named agent at (303) 863-9700.

Respectfully submitted,

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